

PATENT COOPERATION TRLATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/B2004/000910

International filing date (day/month/year)
26.03.2004

Priority date (day/month/year)
27.03.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/675, A61K31/4415, A61K31/4353, A61K31/4355, A61P9/10

Applicant
MEDICURE INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized Officer

Collura, A

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/IB2004/000910

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/B2004/000910

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-49 (with respect to IA)

because:

- ☒ the said international application, or the said claims Nos. 1-49 (with respect to IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/B2004/000910

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-49
	No: Claims	1
Inventive step (IS)	Yes: Claims	2-49
	No: Claims	1
Industrial applicability (IA)	Yes: Claims	-
	No: Claims	-

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-49 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: WO 2004/017916 A (4LIFE RES LC) 4 March 2004 (2004-03-04)
- D2: CHASAN-TABER LISA ET AL: "A prospective study of folate and vitamin B-6 and risk of myocardial infarction in US physicians" JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, vol. 15, no. 2, 1996, pages 136-143, XP009033690 ISSN: 0731-5724
- D3: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1982, URBAIN M ET AL: "POTENTIAL CARDIO VASCULAR AGENTS PIPERAZINO ISO PROPANOL OXY PYRIDOXINES" XP001194600 Database accession no. PREV198375012955
- D4: GB-A-2 075 983 (LABAZ NV) 25 November 1981 (1981-11-25)
- D5: US-A-4 374 841 (DESCAMPS MARCEL ET AL) 22 February 1983 (1983-02-22)
- D6: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1985, WOLF C ET AL: "PIRIDOXILATE AN IMPORTANT LITHOGENIC FACTOR OF CALCIUM OXALATE URINARY STONES" XP009033692 Database accession no. PREV198682029669
- D7: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 1 February 1988 (1988-02-01), RUDZITE V ET AL: "[Peculiarities of nicotinic acid formation in coronary heart disease with special reference to heart arrhythmias]" XP009033693 Database accession no. NLM3369217
- D8: WO 01/64692 A (MEDICURE INTERNAT INC) 7 September 2001 (2001-09-

07)

For what concerns the most relevant paragraphs of the above-mentioned documents, please see citations in the International Search Report, unless otherwise indicated.

1. CLAIM 1

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

As a matter of fact, D1 already discloses the administration of a pharmaceutical composition comprising pyridoxine to a patient suffering from angina.

As well, D2 describes a prospective study, in a model for controlling diabetes, angina, hypertension, Quetelet's index and cholesterol, which shows the role played by pyridoxal phosphate (PLP) in preventing myocardial infarction which prevalently leads to angina.

2. CLAIMS 2, 11, 26, 34 AND 41

Present independent claims 2, 11, 26, 34 and 41 seem to meet the criteria of Article 33(1) PCT, because their subject-matter appears to be new in the sense of Article 33(2) PCT and inventive in the sense of Article 33(3) EPC.

None of the prior art documents seems to anticipate or suggest the claimed subject-matter, the reasons being as follows:

a) D3, D4, D5 and D6 disclose the antiadrenergic activity of molecules derived from pyridoxine which renders them potentially useful as antianginal agents.

Although similar, said compounds are not falling in the general formulas claimed in the present application;

b) D7 teaches that coronary heart problems like angina are often bound to a lack of pyridoxal-5-phosphate (PLP) in the body of patients. However, no therapeutic application of PLP is suggested;

c) D8 discloses many of the compounds claimed in the present application for the treatment of cardiovascular related diseases. However, neither the antianginal nor the antiadrenergic activity of said compounds is described.

The subject-matter of claims 2, 11, 26, 34 and 41 seems, therefore, to be new and inventive since no available prior art document is disclosing exactly or suggesting the claimed subject-matter.

Claims 3-10, 12-25, 27-33, 35-40 and 42-49 are dependent on claims 2, 11, 26, 34 and 41 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

3. INDUSTRIAL APPLICATION

For the assessment of the present claims 1-49 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 12695.17WOU1	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, Item 5 below.</small>	
International application No. PCT/IB2004/000910	International filing date (day/month/year) 26/03/2004	(Earliest) Priority Date (day/month/year) 27/03/2003
Applicant MEDICURE INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 07 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

COMPOSITIONS FOR TREATING ANGINA

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2004/000910

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/675 A61K31/4415 A61K31/4353 A61K31/4355 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/017916 A (4LIFE RES LC) 4 March 2004 (2004-03-04)	1
P,A	page 8 page 12, line 9 - line 14	2-49
X	CHASAN-TABER LISA ET AL: "A prospective study of folate and vitamin B-6 and risk of myocardial infarction in US physicians" JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, vol. 15, no. 2, 1996, pages 136-143, XP009033690 ISSN: 0731-5724	1
A	the whole document ----- -/--	2-49

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

19 July 2004

Date of mailing of the international search report

26/07/2004

Name and mailing address of the ISA

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Authorized officer

Collura, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2004/000910

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1982, URBAIN M ET AL: "POTENTIAL CARDIO VASCULAR AGENTS PIPERAZINO ISO PROPANOL OXY PYRIDOXINES" XP001194600 Database accession no. PREV198375012955 abstract & EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 17, no. 4, 1982, pages 359-364, ISSN: 0223-5234 page 359</p>	1-49
A	<p>GB 2 075 983 A (LABAZ NV) 25 November 1981 (1981-11-25) page 2, line 13 - line 26 page 5, line 8 - line 14 claim 10</p>	1-49
A	<p>US 4 374 841 A (DESCAMPS MARCEL ET AL) 22 February 1983 (1983-02-22) abstract column 2, line 57 - line 63</p>	1-49
A	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1985, WOLF C ET AL: "PIRIDOXILATE AN IMPORTANT LITHOGENIC FACTOR OF CALCIUM OXALATE URINARY STONES" XP009033692 Database accession no. PREV198682029669 abstract & NEPHROLOGIE, vol. 6, no. 5, 1985, pages 225-227, XP009033692 ISSN: 0250-4960 abstract</p>	1-49
A	<p>DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 1 February 1988 (1988-02-01), RUDZITE V ET AL: "'Peculiarities of nicotinic acid formation in coronary heart disease with special reference to heart arrhythmias!" XP009033693 Database accession no. NLM3369217 abstract</p> <p style="text-align: center;">-/--</p>	1-49

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000910

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>& ZEITSCHRIFT FUR DIE GESAMTE INNERE MEDIZIN UND IHRE GRENZGEBIETE ... 1 FEB 1988, vol. 43, no. 3, 1 February 1988 (1988-02-01), pages 60-65, ISSN: 0044-2542 page 61, right-hand column, paragraph 2 ----- WO 01/64692 A (MEDICURE INTERNAT INC) 7 September 2001 (2001-09-07) the whole document -----</p>	1-49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/000910

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-49 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2004/000910

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004017916	A	04-03-2004	WO 2004017916 A2 US 2004126432 A1	04-03-2004 01-07-2004
GB 2075983	A	25-11-1981	AR 226356 A1 AT 3859 T AU 542463 B2 AU 7053581 A BG 35327 A3 CA 1152080 A1 CS 223842 B2 DD 159071 A5 DE 3160480 D1 DK 217481 A EG 15890 A EP 0040591 A1 ES 8203845 A1 FI 811525 A GR 82343 A1 HU 183441 B IE 51179 B1 IL 62602 A IN 151915 A1 JP 57011966 A MA 19147 A1 MX 6323 E NO 811680 A NZ 196766 A OA 6811 A PL 231193 A1 PT 72992 A , B RO 81943 A1 SU 1077566 A3 US 4374841 A YU 126281 A1 ZA 8102448 A ZW 9681 A1	30-06-1982 15-07-1983 21-02-1985 26-11-1981 15-03-1984 16-08-1983 25-11-1983 16-02-1983 28-07-1983 20-11-1981 30-03-1987 25-11-1981 16-07-1982 20-11-1981 13-12-1984 28-05-1984 29-10-1986 29-06-1984 03-09-1983 21-01-1982 31-12-1981 01-04-1985 20-11-1981 03-02-1984 31-12-1982 05-07-1982 01-06-1981 01-06-1983 29-02-1984 22-02-1983 29-02-1984 28-04-1982 20-01-1982
US 4374841	A	22-02-1983	AR 226356 A1 AT 3859 T AU 542463 B2 AU 7053581 A BG 35327 A3 CA 1152080 A1 CS 223842 B2 DD 159071 A5 DE 3160480 D1 DK 217481 A EG 15890 A EP 0040591 A1 ES 8203845 A1 FI 811525 A GB 2075983 A , B GR 82343 A1 HU 183441 B IE 51179 B1 IL 62602 A IN 151915 A1 JP 57011966 A	30-06-1982 15-07-1983 21-02-1985 26-11-1981 15-03-1984 16-08-1983 25-11-1983 16-02-1983 28-07-1983 20-11-1981 30-03-1987 25-11-1981 16-07-1982 20-11-1981 25-11-1981 13-12-1984 28-05-1984 29-10-1986 29-06-1984 03-09-1983 21-01-1982

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2004/000910

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4374841	A		MA 19147 A1	31-12-1981
			MX 6323 E	01-04-1985
			NO 811680 A	20-11-1981
			NZ 196766 A	03-02-1984
			OA 6811 A	31-12-1982
			PL 231193 A1	05-07-1982
			PT 72992 A , B	01-06-1981
			RO 81943 A1	01-06-1983
			SU 1077566 A3	29-02-1984
			YU 126281 A1	29-02-1984
			ZA 8102448 A	28-04-1982
			ZW 9681 A1	20-01-1982
<hr/>				
WO 0164692	A	07-09-2001	AU 3718501 A	12-09-2001
			WO 0164692 A1	07-09-2001
			CA 2401655 A1	07-09-2001
			EP 1268498 A1	02-01-2003
			JP 2003525303 T	26-08-2003
			US 2003114677 A1	19-06-2003
			US 2003114678 A1	19-06-2003
			US 2003120074 A1	26-06-2003
			US 2003181422 A1	25-09-2003
			US 2002010158 A1	24-01-2002